Br. J. Pharmac. (1987), **92**, 221–229

Influence of thyroid status on responses of rat isolated pulmonary artery, vas deferens and trachea to smooth muscle relaxant drugs

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1 Responses to relaxant drugs have been examined on isolated KCl-contracted smooth muscle preparations from rats in which thyroid status was changed by prior treatment with either thyroxine (T_4) for 1 week (preparations of pulmonary artery, trachea and vas deferens) or methimazole for 10–12 weeks (pulmonary artery preparations).

2 On pulmonary artery preparations, T_4 treatment caused a significant increase in the magnitude of the relaxant responses to noradrenaline and isoprenaline but not those to adrenaline. The potency of noradrenaline was increased 5.6 fold but that of isoprenaline and adrenaline was unchanged. This resulted in a change in the relative potencies from adrenaline > noradrenaline (controls) to noradrenaline = adrenaline (T_4-treated). Methimazole treatment caused a significant reduction in the magnitude of the responses to noradrenaline and in its potency (2.8 fold). Isoprenaline and procaterol were unaffected.

3 On pulmonary artery preparations, T_4 treatment did not affect the magnitude of the responses to forskolin, sodium nitrite or isobutylmethylxanthine (IBMX) or their potency. *In vitro* treatment with the monoamine oxidase (MAO) inhibitors, iproniazid or pargyline, did not potentiate responses to either noradrenaline or isoprenaline. Therefore, it was concluded that the T_4-induced changes in the magnitude of the responses to noradrenaline and isoprenaline and in the potency of noradrenaline were unlikely to be due to reduced activity of cyclic nucleotide phosphodiesterase(s) or MAO.

4 On preparations of vas deferens and trachea, T_4 treatment had no effect on the magnitude of the responses to noradrenaline, isoprenaline, adrenaline or procaterol. On preparations of trachea, but not vas deferens, T_4 treatment significantly increased the potency of noradrenaline (2.9 fold) but not that of isoprenaline, adrenaline or procaterol.

5 We concluded that, on pulmonary artery T_4 treatment of rats increased, while methimazole treatment reduced, the magnitude of the responses to, and/or the potency of, the β-adrenoceptor agonists, noradrenaline and isoprenaline, by a mechanism which is specifically associated with the β-adrenoceptors, and which is probably selective for the β_1-subtype. T_4 treatment caused no change in responses of vas deferens to β-adrenoceptor agonists. On trachea the only change was a small increase in the potency of noradrenaline. The differences in the effects of T_4 treatment on β-adrenoceptor-mediated responses of rat pulmonary artery, vas deferens and trachea may be due to the differences in the β-adrenoceptor populations of these three tissue types and/or differences in the effects of thyroid hormones on vascular compared with non-vascular smooth muscle.

Introduction

In isolated, KCl-contracted preparations of pulmonary artery and aorta taken from rats treated with thyroxine (T_4) for 3–5 weeks, β-adrenoceptor-mediated relaxant responses to noradrenaline and isoprenaline, but not adrenaline, fenoterol or procaterol, were increased, compared with responses of preparations from saline-treated control rats (O'Donnell & Wanstall, 1986). Furthermore, the order of potency of the three catecholamine β-adrenoceptor agonists changed from isoprenaline > adrenaline > noradrenaline (controls) to isoprenaline

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> noradrenaline ≥ adrenaline (T_4-treated, O'Donnell & Wanstall, 1986). These observations have been followed up in the present study which has examined: (a) whether the change in the order of potency of adrenaline and noradrenaline was seen on preparations of pulmonary artery taken from rats which received a shorter-term treatment with T_4 (i.e. for 1 week); (b) whether the effect of T_4 treatment on the responses of pulmonary artery to noradrenaline and isoprenaline occurred at the β-adrenoceptors, or was due to inhibition, by T_4, of the activity of phosphodiesterase and/or monoamine oxidase (MAO); (c) whether treatment of rats with methimazole produced effects opposite to those produced by T_4 treatment; and (d) whether enhancement of β-adrenoceptor-mediated responses could be seen on non-vascular smooth muscle preparations (i.e. vas deferens and trachea) from T_4-treated rats.

A preliminary account of some of these data has been presented to the symposium on 'The Pharmacology of Adrenoceptors' Manchester, 1984 (O'Donnell *et al.*, 1985), and to the 18th meeting of the Australasian Society of Clinical and Experimental Pharmacologists, Melbourne 1984 (Mustafa *et al.*, 1985).

Methods

Male Wistar rats, weighing 100 to 300 g at the time of the experiments, were used throughout the study. Treated rats (*vide infra*) and the corresponding controls were age- and weight-matched at the start of treatment.

Treatment of rats with thyroxine

Rats were 5 to 6 weeks old at the start of the treatment.They were given s.c. injections of either the sodium salt of thyroxine (1 mg kg^{-1} i.e. 1 ml kg^{-1} of a 1 mg ml^{-1} suspension in saline) or saline (1 ml kg^{-1}, controls) on days, 1, 3 and 5 and were used for the isolated tissue experiments on day 8.

Treatment of rats with methimazole

Rats were 4 weeks old at the start of the treatment and were given methimazole (0.05% w/v) in their drinking water (*ad libitum*) for 10 to 12 weeks. Control rats received normal drinking water for the same period of time.

Assessment of thyroid status

Body weight, thyroid weight and serum T_4 and triiodothyronine (T_3) levels were determined as described previously (O'Donnell & Wanstall, 1986). In addition, for the T_4-treated rats and their controls, heart wet weight was recorded on the day of the experiment.

Rats on either T_4 treatment or methimazole treatment gained less weight during the treatment period than the corresponding control rats. T_4 treatment caused significant increases in serum T_4 and T_3 levels (Table 1). There was also a small, but not statistically significant, decrease in thyroid weight relative to body weight (Table 1), and a 40% increase ($P < 0.001$; Student's t test) in heart weight relative to body weight. Methimazole treatment caused significant decreases in serum T_4 and T_3 levels and a significant increase in thyroid weight (Table 1).

Isolated tissue preparations

Isolated, single ring preparations of pulmonary artery or trachea (resting tension 1 g) were set up in Krebs solution at 37°C to record changes in tension of the circular muscle (O'Donnell & Wanstall, 1981). Preparations of the epididymal half of the vas deferens (resting tension 500 mg) were set up in Krebs solution at 37°C to record changes in tension of the longitudinal muscle. The composition of the Krebs solution was (mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, glucose 11.7, ascorbic acid 1.1.

All isolated tissue preparations were pre-exposed to phenoxybenzamine (50 μM for 30 min followed by washout) to block α-adrenoceptors and neuronal and extraneuronal uptakes, and were submaximally contracted with KCl (15 mM on pulmonary artery and 45 mM on trachea or vas deferens). These concentrations gave contractions which were 50%–60% of the maximum contractile response to KCl in each tissue type. Once the KCl-induced contraction had stabilized, i.e. after 5–10, 15–20 and 20–25 min in pulmonary artery, vas deferens and trachea, respectively, cumulative concentration-response curves were obtained to relaxant drugs. In the absence of any relaxant drug, there was no spontaneous decline in the KCl-induced contractions over the periods of time required to complete a concentration-response curve to a relaxant drug (i.e. approximately 20, 25 and 40 min on pulmonary artery, vas deferens and trachea, respectively). The size of the contractions induced by KCl were (g):- pulmonary artery control 0.22 ± 0.01 ($n = 34$), T_4-treated 0.38 ± 0.02 (36) ($P < 0.001$, Student's t test, control vs. T_4-treated); vas deferens control 0.32 ± 0.03 (18), T_4-treated 0.30 ± 0.03 (14) ($P > 0.05$); trachea control 1.09 ± 0.09 (20), T_4-treated 0.73 ± 0.03 (20) ($P < 0.001$).

Responses to the relaxant drugs were expressed as % reversal of the KCl-induced contractions. The maximal relaxation was sometimes greater than 100% indicating that some of the preparations had some

Table 1 Thyroid weight and total serum T_4 and T_3 concentrations for control rats and rats treated with T_4 or methimazole

	Thyroid weight (mg 100 g^{-1} body wt.)	*Total serum T_4* (ng ml^{-1})	*Total serum T_3* (ng ml^{-1})
Saline-treated (controls)	7.8 ± 0.5 (14)	48.9 ± 4.8 (14)	0.98 ± 0.06 (14)
T_4-treated[a]	6.6 ± 0.4 (17)	201.8 ± 13.4*** (17)	3.65 ± 0.31*** (17)
Normal drinking water (controls)	6.4 ± 0.6 (5)	55.2 ± 2.0 (5)	1.12 ± 0.08 (5)
Methimazole in drinking water[b]	27.6 ± 2.0*** (5)	3.3 ± 0.5*** (5)	0.44 ± 0.03*** (5)

Results shown are the mean values ± s.e. with numbers of rats in parenthesis.
[a] T_4 sodium salt, 1 mg kg^{-1} s.c., on days 1, 3 and 5; experiment on day 8.
[b] Methimazole 0.05% in drinking water for 10–12 weeks.
***Significantly different from controls, $P < 0.001$, Student's t test.

inherent tone. Individual concentration-response curves were used to obtain EC_{50} values (i.e. the concentration producing 50% of the maximum response to the particular drug, established at the end of each curve), and the mean negative log EC_{50} was used as an expression of potency. Mean concentration-response curves were drawn using the mean responses, as defined above, at each concentration of relaxant drug used.

In experiments in which two or more β-adrenoceptor agonists were compared on the same preparation, the concentration-response curves to the different agonists were obtained in random order in different experiments. In experiments in which the effects of inhibition of monoamine oxidase (MAO) were investigated, concentration-response curves to isoprenaline and noradrenaline were obtained before and after treatment of the tissues *in vitro* with iproniazid 500 μM for 30 min followed by washout) or pargyline (500 μM for 15 min followed by washout). On separate preparations repeated concentration-response curves to isoprenaline and noradrenaline were shown to be reproducible; the mean differences between negative log EC_{50} values in the first and second curves were:- isoprenaline 0.06 ± 0.05 log units ($n = 5$), noradrenaline 0.08 ± 0.03 log units ($n = 7$). In the experiments with sodium nitrite, isobutylmethylxanthine (IBMX) and forskolin, sodium nitrite and IBMX were examined on the same preparations (in random order), while forskolin was examined on separate preparations. In each of these experiments a concentration-response curve to noradrenaline was obtained before the curve(s) to the test drug(s).

Drugs and solutions

The following drugs were used:- (−)-adrenaline acid tartrate (Sigma); forskolin (Calbiochem-Behring); iproniazid phosphate (Sigma); 3-isobutyl-1-methyl xanthine (IBMX, Sigma); (−)-isoprenaline acid tartrate (Sigma); methimazole (Sigma); (−)-noradrenaline acid tartrate (Sigma); pargyline hydrochloride (Sigma); phenoxybenzamine hydrochloride (Smith, Kline & French); procaterol (Warner Lambert); sodium nitrite (B.D.H. Chemicals); L-thyroxine sodium salt (Sigma). Radioimmunoassay kits for T_4 and T_3 assays were kindly provided by Nuclear Diagnostics, Sydney.

Stock solutions (100 mM) of adrenaline, isoprenaline and noradrenaline were made up in 10 mM HCl. Iproniazid (100 mM), pargyline (100 mM), procaterol (10 mM) and sodium nitrite (1 M) were made up in deionised water immediately before use. Phenoxybenzamine (100 mM) was dissolved in absolute ethanol containing 10 mM HCl. IBMX (10 mM) was made up in 10 mM NaOH. Forskolin was dissolved and diluted in absolute ethanol. Dilutions of other drugs were made in Krebs solution and kept on ice during the course of the experiment. Suspensions of thyroxine (sodium salt; 1 mg ml^{-1}) were made in 0.9% saline. Methimazole was dissolved in the rats' normal drinking water.

Statistical analyses

Mean values of negative log EC_{50}, serum T_4 and T_3 levels and thyroid weight are quoted together with the standard error (s.e.) of the mean. The significance of differences between these mean values was assessed by Student's t test. The significance of the differences between mean values of response (expressed as % reversal of KCl-induced contraction) was assessed by the Mann-Whitney test (Snedecor & Cochran, 1967). For these mean values standard errors have been included in the figures only to indicate the variation in the data.

Results

Pulmonary artery preparations: effects of T_4 treatment of rats

On pulmonary artery preparations taken from rats treated with T_4 for 1 week, there was a statistically significant ($P < 0.05$; Mann Whitney test) increase in the magnitude of the relaxant responses (compared with controls) to all the concentrations of noradrenaline (Figure 1a), and to two of the concentrations of isoprenaline (8 and 32 nM). There was no increase in responses to adrenaline (40 nM to 2.6 μM) or isoprenaline (2 nM, 130 nM and 10 μM). There was also a statistically significant increase in the potency (mean negative log EC_{50}) of noradrenaline (5.6 fold) but not of adrenaline or isoprenaline (Table 2) and this resulted in a change in their relative potencies from adrenaline > noradrenaline (controls) to noradrenaline = adrenaline (T_4-treated, Table 2). We obtained a similar result previously using a longer period of T_4 treatment (3 to 5 weeks, O'Donnell & Wanstall, 1986).

T_4 treatment of rats did not affect the magnitude of the relaxant responses to, or the potency of, sodium nitrite, forskolin or IBMX, i.e. the concentration-response curves on preparations from control and T_4-treated rats were superimposed (Figure 1 b, c, d), even though the magnitude of the responses to, and the potency of, noradrenaline were enhanced on the same preparations (Figure 1a). The mean negative log EC_{50} values corresponding to the data in Figure 1 b, c and d were (control, T_4-treated):- sodium nitrite 4.45 ± 0.06, 4.38 ± 0.02; forskolin 7.40 ± 0.08, 7.46 ± 0.12, IBMX 5.89 ± 0.15, 5.58 ± 0.19.

Pulmonary artery preparations: effects of methimazole treatment of rats

On preparations of pulmonary artery from methimazole-treated rats ($n = 5$), there was a significant

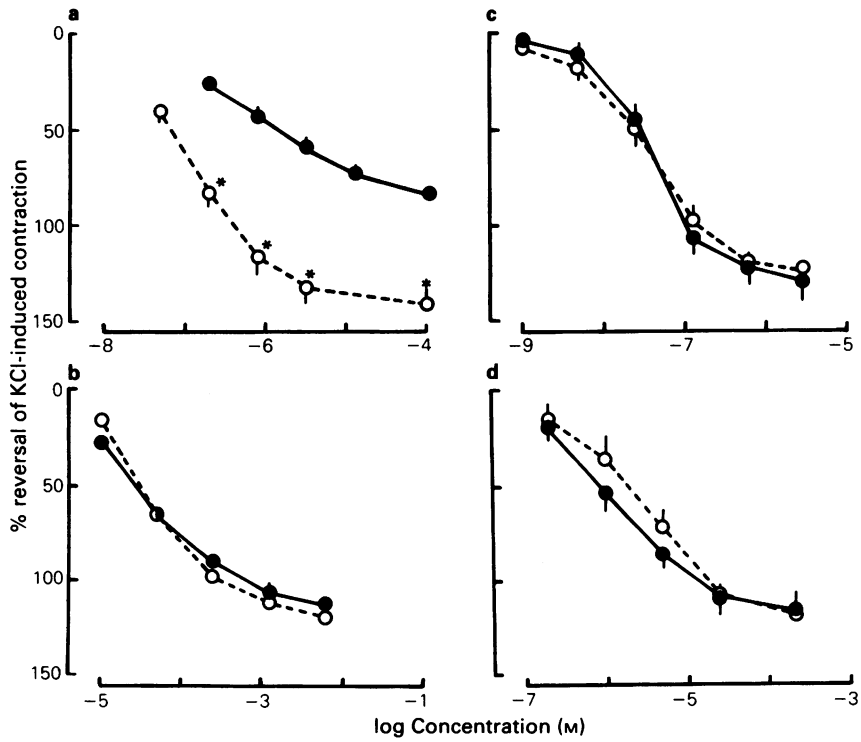

Figure 1 Pulmonary artery preparations. Mean concentration-response curves to noradrenaline (a), sodium nitrite (b), forskolin (c) and isobutylmethylxanthine (d) on preparations from control (●) and T_4-treated (○) rats. Responses are expressed as % reversal of the KCl-induced contractions. Standard errors of the mean responses (except when smaller than the symbols) are shown by the vertical lines. Numbers of rats (saline-treated, T_4-treated, respectively) were: (a) 8, 9; (b) 4, 4; (c) 4, 5 and (d) 4, 4. Statistical comparisons between saline- and T_4-treated rats were made by use of the Mann-Whitney test (*$P < 0.01$).

Table 2 Potency (negative log EC_{50} values) of β-adrenoceptor agonists on preparations of pulmonary artery, vas deferens and trachea from saline-treated (control) and T_4-treated rats

	− log EC_{50}				*Relative potency* (A : NA)
	Noradrenaline (NA)	*Adrenaline* (A)	*Isoprenaline*	*Procaterol*	
Pulmonary artery					
Control	6.08 ± 0.16 (6)	6.94 ± 0.12 (4)	7.87 ± 0.13 (4)		7.2:1
T_4-treated[a]	6.83 ± 0.06** (4)	6.93 ± 0.04 (4)	8.12 ± 0.08 (4)		1.3:1
Vas deferens					
Control	5.15 ± 0.04 (5)	6.89 ± 0.07 (5)	7.67 ± 0.07 (5)	7.60 ± 0.07 (3)	55:1
T_4-treated[a]	5.05 ± 0.10 (4)	6.81 ± 0.04 (3)	7.66 ± 0.05 (4)	7.61 ± 0.04 (3)	58:1
Trachea					
Control	6.24 ± 0.10 (5)	6.39 ± 0.06 (5)	7.46 ± 0.08 (5)	7.16 ± 0.05 (5)	1.4:1
T_4-treated[a]	6.71 ± 0.13* (5)	6.53 ± 0.08 (5)	7.70 ± 0.13 (5)	7.29 ± 0.10 (5)	0.66:1

Results shown are mean values ± s.e. with numbers of observations in parentheses. All preparations were treated with phenoxybenzamine (50 μM) for 30 min followed by washout.

[a] Rats treated with T_4 (sodium salt), 1 mg kg^{-1} s.c., on days 1, 3 and 5, experiment on day 8. Asterisks indicate that the value for T_4-treated rats was significantly different from the corresponding value for control rats: *$0.05 > P > 0.01$; **$0.01 > P > 0.001$ (Student's t test).

reduction in the magnitude of the relaxant responses to noradrenaline ($P < 0.05$, Mann-Whitney test) and a reduction in the potency of noradrenaline (mean negative log EC_{50} values:- control 5.64 ± 0.13; methimazole-treated 5.20 ± 0.13; $0.05 > P > 0.01$, Student's t test). Neither of these changes occurred with isoprenaline or procaterol (mean negative log EC_{50} values:- isoprenaline control 7.86 ± 0.06; methimazole-treated 7.77 ± 0.08, $P > 0.05$, procaterol control 7.62 ± 0.02; methimazole-treated 7.62 ± 0.07, $P > 0.05$).

Pulmonary artery preparations: effects of monoamine oxidase inhibitors in vitro

The *in vitro* treatment of pulmonary artery preparations with either iproniazid (Figure 2) or pargyline (data not shown) had no effect on the magnitude of the

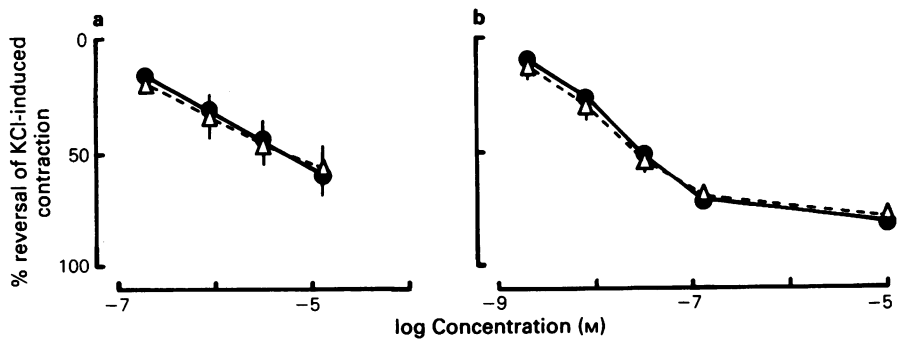

Figure 2 Mean concentration-response curves ($n = 3$) to (a) noradrenaline and (b) isoprenaline on preparations of rat pulmonary artery. Data before (●) and after (△) treatment of the tissues with iproniazid (500 μM for 30 min followed by washout) are shown. Responses and standard errors are as in Figure 1.

relaxant responses to either noradrenaline or isoprenaline i.e. the concentration-response curves before and after treatment of the tissues with the MAO inhibitors were superimposed.

Vas deferens and tracheal preparations: effects of T_4 treatment of rats

On preparations of vas deferens, T_4 treatment did not affect the magnitude of the relaxant responses to noradrenaline, adrenaline, isoprenaline or procaterol (Figure 3), nor the potencies or relative potencies of these β-adrenoceptor agonists (Table 2).

On preparations of trachea, T_4 treatment caused small increases in the magnitudes of the relaxant responses to noradrenaline, adrenaline and isoprenaline, but these were not statistically significant (Figure 4). There was a small (2.9 fold) increase in the potency of noradrenaline, but not of the other three agonists, and only a small change in the relative potencies of noradrenaline and adrenaline (Table 2).

Discussion

In a previous study it was demonstrated that, on isolated pulmonary artery, the magnitude of β-adrenoceptor-mediated relaxant responses to noradrenaline and isoprenaline was greater in preparations from T_4-treated rats than in those from control rats (O'Donnell & Wanstall, 1986). In the present study the period of treatment of the rats with T_4 has been reduced from 3–5 weeks (O'Donnell & Wanstall, 1986) to 1 week, but this did not change the effects of the T_4 treatment: circulating T_4 and T_3 levels were still 4 fold higher than in controls; β-adrenoceptor-mediated responses of pulmonary artery to noradrenaline and isoprenaline still increased in magnitude; and noradrenaline still became equipotent with adrenaline, as opposed to less potent than adrenaline in controls. Thus tissues used in the present study were taken from rats treated with T_4 for one week.

In the present study T_4 treatment of rats did not affect the magnitude of responses of pulmonary artery

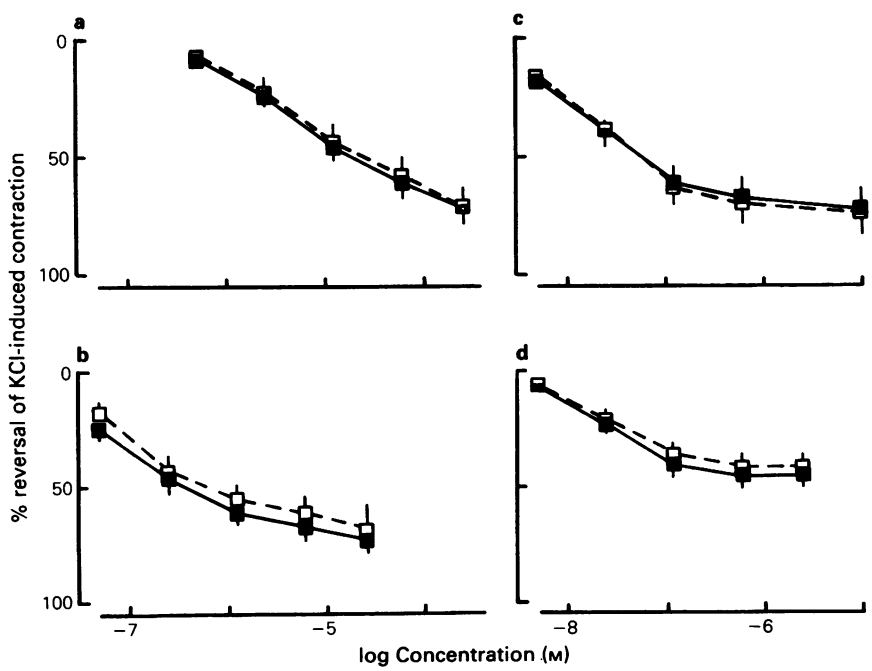

Figure 3 Vas deferens preparations. Mean concentration-response curves to noradrenaline (a), adrenaline (b), isoprenaline (c) and procaterol (d) on preparations from saline-treated control (■) and T_4-treated (□) rats. Responses and standard errors are as in Figure 1. Numbers of rats (saline-treated, T_4 treated, respectively) were: (a) 5, 4; (b) 5, 3; (c) 5, 4 and (d) 3, 3. There were no significant differences between saline- and T_4-treated rats ($P > 0.05$, Mann-Whitney test).

preparations to forskolin (adenylate cyclase activator), IBMX (phosphodiesterase inhibitor) or sodium nitrite (which increases cyclic GMP), whereas responses to noradrenaline were increased on the same preparations. These data show that the increase in the magnitude of β-adrenoceptor-mediated responses to noradrenaline and isoprenaline (*vide supra*) cannot be due to (a) a reduction in phosphodiesterase activity, even though thyroid hormones are known to inhibit cyclic nucleotide phosphodiesterases (van Inwegen *et al.*, 1975; Tse *et al.*, 1980), (b) a non-specific increase in the ability of the vascular smooth muscle to relax, or (c) the increase in the magnitude of the KCl-induced contractions seen in preparations from T_4-treated rats in the present study (see Methods). If a reduction in phosphodiesterase activity had been the explanation for the increased responses to noradrenaline and isoprenaline, then T_4 treatment would also have increased responses to other relaxant drugs which act via cyclic nucleotides including forskolin, IBMX and sodium nitrite. If a non-specific increase in vascular relaxation or the increase in the size of the KCl-induced contractions had been the explanation, then vascular relaxant drugs other than β-adrenoceptor agonists, e.g. forskolin, IBMX and sodium nitrite, would also have been affected. It is also relevant to note that the increases in the responses to the β-adrenoceptor agonists, noradrenaline and isoprenaline, were seen in both this and our previous study (O'Donnell & Wanstall, 1986), whereas a significant change in the size of the KCl-induced contractions was seen only in the present study. This observation supports the view that the changes in responses to noradrenaline or isoprenaline were probably unrelated to any changes in the size of the KCl-induced contractions.

It was also possible that a reduction in MAO activity could explain the increase in the relaxant responses to noradrenaline in preparations from T_4-treated rats, since thyroid hormones have been shown to inhibit MAO activity, at least in some tissues (Spinks & Burn, 1952; Bryan *et al.*, 1986), and, in some blood vessel preparations noradrenaline can be potentiated by MAO inhibitors (Kalsner & Nickerson, 1969). This possibility was not supported by the data from the present study in that the effect of noradrenaline was not potentiated by *in vitro* treatment of the pulmonary artery preparations with iproniazid or pargyline i.e. the effects of T_4 treatment of rats on responses of pulmonary artery to noradrenaline were not mimicked by *in vitro* treatment of the tissues with MAO inhibitors. The most likely explanation for the

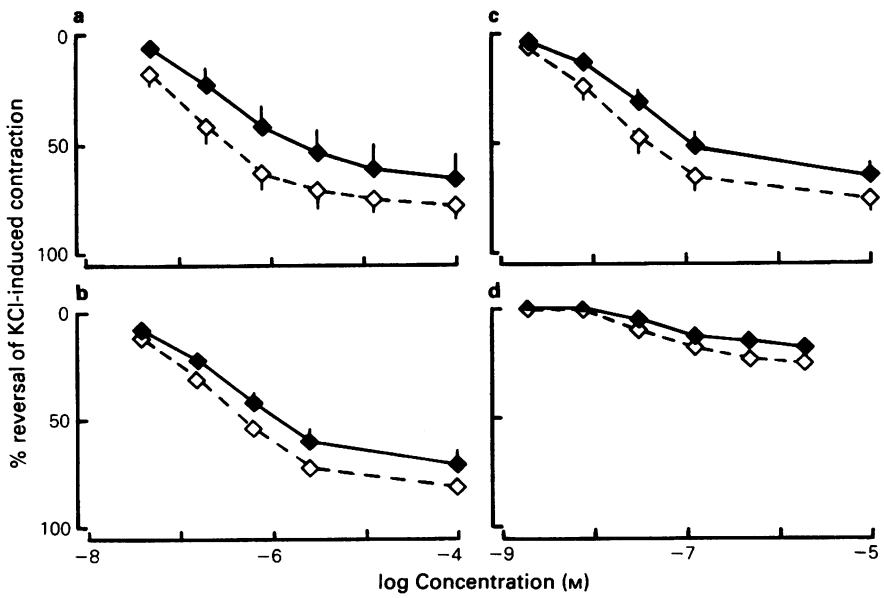

Figure 4 Tracheal preparations. Mean concentration-response curves to noradrenaline (a), adrenaline (b), isoprenaline (c) and procaterol (d) on preparations from saline-treated control (◆) and T_4-treated (◇) rats. Responses and standard errors are as in Figure 1. Numbers of rats were 5 for saline-treated and T_4-treated. There were no significant differences between saline- and T_4-treated rats ($P > 0.05$, Mann-Whitney test).

results with noradrenaline and isoprenaline on pulmonary artery from T_4-treated rats was that T_4-treatment directly influenced β-adrenoceptors, possibly by increasing the number of receptors and/or their coupling to adenylate cyclase. This has been shown to occur in other tissues (Williams *et al.*, 1977; Stiles & Lefkowitz, 1981; Stiles *et al.*, 1984; Gross & Lues, 1985; Fox *et al.*, 1986).

The effects of reducing circulating thyroid hormones on β-adrenoceptor-mediated responses in various tissues are frequently opposite to the effects of increasing thyroid hormones (Stiles *et al.*, 1984; Gross & Lues, 1985; Fox *et al.*, 1986). Thus, in the present study, the influence of methimazole treatment of rats on responses of pulmonary artery to β-adrenoceptor agonists was examined. Methimazole treatment lowered circulating thyroid hormones, and reduced the magnitude of the responses to, and the potency of, noradrenaline, but not that of isoprenaline or procaterol i.e. it had the opposite effect to T_4 treatment. In addition, both methimazole treatment and T_4 treatment selectively influenced noradrenaline (a β_1-selective agonist), compared with the other β-adrenoceptor agonists examined. This observation is compatible with our previous suggestion that changes in thyroid status may affect β_1-adrenoceptor-mediated responses more than β_2-adrenoceptor-mediated responses (O'Donnell & Wanstall, 1986).

It was therefore of interest to compare the effects of T_4 treatment on rat tissues with different β-adrenoceptor populations *viz* pulmonary artery, vas deferens and trachea. Rat pulmonary artery contains both β-adrenoceptor subtypes with the β_2-subtype predominating (O'Donnell & Wanstall, 1981). Rat vas deferens has a homogeneous population of β_2-adrenoceptors (Krstew *et al.*, 1982; May *et al.*, 1985; supported by relative potency values in the present study), while rat trachea contains both β-adrenoceptor subtypes (Henry *et al.*, 1981) with the β_1-subtype predominating (refer relative potency values in the present study). Comparison of these three tissues provided several results which were compatible with the hypothesis that T_4 treatment affects the β_1-adrenoceptor subtype: (a) T_4 treatment had no effect on responses of trachea, vas deferens (present study) or pulmonary artery (O'Donnell & Wanstall, 1986) to the β_2-selective agonist procaterol (in concentrations which activate only β_2-adrenoceptors i.e. $< 1\ \mu M$, O'Donnell & Wanstall, 1985); (b) T_4 treatment had no effect on responses of vas deferens (which contains no β_1-adrenoceptors) to any of the β-adrenoceptor agonists; (c) on trachea, as on pulmonary artery, the only agonist which increased in potency in preparations from T_4-treated rats was noradrenaline (β_1-selective); (d) T_4 treatment changed the relative potencies of noradrenaline and adrenaline on pulmonary artery from adrenaline >noradrenaline (characteristic of β_2-adrenoceptors predominating) to noradrenaline = adrenaline (characteristic of β_1-adrenoceptors predominating). In contrast there was no change in their relative potencies on vas deferens (β_2-adrenoceptors only) and only a very small change on trachea (β_1-adrenoceptors predominant even in controls). However, not all the observations can be explained by the hypothesis that T_4 treatment selectively affects the β_1-adrenoceptor subtype. In particular, the lack of any significant effect of T_4 treatment on responses of trachea to isoprenaline and adrenaline was unexpected. Thus, even if the hypothesis is valid, it appears that the effects of thyroid hormones on β-adrenoceptor-mediated responses also differ quantitatively between tissue types (Taylor, 1983).

In summary, on pulmonary artery (a tissue in which β_2-adrenoceptors predominate), treatment of rats with T_4 increased the magnitude of the responses to the β-adrenoceptor agonists, noradrenaline and isoprenaline, but not adrenaline, increased the potency of noradrenaline, and altered the relative potencies of adrenaline and noradrenaline. Data were obtained which indicate that this effect of T_4 treatment of rats occurred at the β-adrenoceptors and was not the result of a reduction in phosphodiesterase and/or MAO activity. Data on pulmonary artery also showed that the effects of treatment of rats with methimazole were opposite to those of T_4 treatment. In contrast, on vas deferens (a tissue which has a homogeneous population of β_2-adrenoceptors) T_4 treatment did not influence the magnitude of β-adrenoceptor-mediated responses to, or the potency of, noradrenaline, isoprenaline, adrenaline or procaterol. On trachea (a tissue in which, in rats, β_1-adrenoceptors predominate) there was a small increase in the potency of noradrenaline in preparations from T_4-treated rats, but no effect on the magnitude of the responses to noradrenaline, isoprenaline, adrenaline or procaterol. The data are compatible with the suggestions that treating rats with thyroid hormones (a) results in a selective increase in responses mediated by the β_1-adrenoceptor subtype (O'Donnell & Wanstall, 1986) and (b) will not necessarily produce the same effect on β-adrenoceptor-mediated responses in different tissue types (Taylor, 1983).

This work was supported by a grant from the National Health and Medical Research Council of Australia and this aid is gratefully acknowledged. J.C.W. is an NH&MRC Senior Research Officer. We would like to thank Miss Tina Greco for her excellent technical assistance.

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(Received April 17, 1987. Accepted May 5, 1987.)